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(54) Title: COMPOSITIONS COMPRISING FLEXIBLE PARTICLES, NON-IONIC SURFACTANT AND NON-IONIC CLOUD-POINT MODIFIER (57) Abstract A diagnostic or therapeutic composition comprising physiologically tolerable, diagnostically or therapeutically effective flexible particles and a physiologically tolerable non-ionic surfactant emulsifier in an aqueous dispersion medium, characterised in that said aqueous dispersion medium further contains a physiologically tolerable, non-ionic, water-soluble cloud-point modifier at a concentration such that the cloud point of said medium is above a temperature usable for steam sterilization.		

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HL → FYI From Sheena.



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## COMPOSITIONS COMPRISING FLEXIBLE PARTICLES, NON-IONIC SURFACTANT AND NON-IONIC CLOUD-POINT MODIFIER

This invention relates to aqueous pharmaceutical or diagnostic compositions containing flexible particles, eg. emulsion droplets or vesicles, and in particular to formulation improvements which facilitate the heat sterilization of such compositions.

Compositions containing emulsion droplets or flexible vesicles (eg. micelles, liposomes, water-in-oil-in-water emulsions, microbubbles and microballoons) have been proposed for both therapeutic and diagnostic use. Thus for example vesicles may be used to carry or contain diagnostically or therapeutically effective agents, eg. contrast agents for diagnostic imaging modalities such as X-ray, MR, ultrasound, scintigraphy, light imaging, SPECT, PET, magnetotomography and electrical impedance tomography.

Similarly water-insoluble, liquid agents, eg. iodinated contrast media for X-ray imaging, or fluorocarbons for use as oxygen carriers in blood replacements, have been formulated as oil-in-water emulsions.

In the development of such dispersed dosage forms for parenteral use, product sterilization represents a major challenge. The two most common sterilization techniques are sterile filtration and thermal sterilization (eg. autoclaving or steam sterilization). However sterile filtration is not feasible where the desired flexible particle size is in excess of 200 nm which is generally the case with such compositions where particle sizes may be as large as 7  $\mu\text{m}$ . Thermal sterilization is also problematical as it often leads to significant increases in particle size as a result of heat-induced aggregation and/or particle growth.

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Dispersions for parenteral administration generally require the use of a surfactant as an emulsifier or stabilizer, routinely at low concentrations, eg. 2% by weight. Since the presence of ionic excipients can cause particle agglomeration, and may cause toxicity problems and since particle agglomeration is clearly undesirable for parenterally administered compositions, it is clearly desirable to use non-ionic surfactants as emulsifiers (the term "emulsifier" will be used hereinafter to cover such surfactants used as emulsifiers and/or stabilizers in particulate dispersions). The use of non-ionics is further desirable since they impart steric stability. Unfortunately, where a non-ionic surfactant is used as an emulsifier for such flexible particle dispersions, the problems of thermal sterilization are exacerbated as at elevated temperatures such non-ionic surfactants undergo a well-known phase separation (referred to as a cloud point) which may cause the compositions to flocculate or coalesce.

We have however now found that non-ionic surfactant containing dispersions of flexible particles can be stabilized for thermal sterilization by the inclusion in the dispersion medium of a non-ionic water-soluble cloud point modifier at a concentration such that the cloud point of the dispersion medium is above the temperature used for steam sterilization, ie. generally 121°C or above. Such modifiers are also useful for steam sterilization of such dispersions at lower temperatures, eg. at 90°C.

Thus viewed from one aspect the invention provides a diagnostic or therapeutic composition comprising physiologically tolerable, diagnostically or therapeutically effective flexible particles and a physiologically tolerable non-ionic surfactant emulsifier in an aqueous dispersion medium,

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characterised in that said aqueous dispersion medium further contains a physiologically tolerable non-ionic water-soluble cloud point modifier at a concentration such that the cloud point of said medium is above a temperature usable for steam sterilization, preferably above the temperature required for sterilization, usually 121°C or above.

Viewed from a further aspect the invention provides a process for the preparation of a sterile aqueous dispersion, said process comprising steam heat sterilizing (eg. by autoclaving) a composition comprising physiologically tolerable, diagnostically or therapeutically effective flexible particles, and a physiologically tolerable non-ionic surfactant emulsifier in an aqueous dispersion medium, characterised in that said aqueous dispersion medium further contains a physiologically tolerable non-ionic water-soluble cloud point modifier at a concentration such that the cloud point of said medium is above the steam sterilization temperature, preferably above 121°C.

Viewed from a yet still further aspect the invention provides the use of heat sterilized compositions according to the invention in therapy or diagnosis, eg. in a diagnostic imaging procedure.

Non-ionic, water-soluble cloud point modifiers useful according to the invention include poly(ethylene glycols) (eg. PEG 300, PEG 400, PEG 1000, PEG 1450 and PEG 2000, preferably PEG 1450), propylene glycols, monoalcohols (such as methanol, ethanol and isopropanol), polyols (such as sorbitol, mannitol and glycerol) and cyclodextrins. The compositions according to the invention may contain a single non-ionic cloud point modifier or a mixture of two or more non-ionic cloud point modifiers.

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The quantity of non-ionic cloud point modifier used will depend upon the nature and quantity of the other excipients present in the dispersion medium but will be a quantity sufficient to raise the cloud point above the temperature required for sterilization. The necessary amount may readily be determined by the person of ordinary skill in pharmaceutical science. Generally the amount will be in the range 0.1 to 50% by weight (relative to the weight of the aqueous phase of the composition), particularly 1 to 30%, more particularly 5 to 20%.

The non-ionic surfactant emulsifiers used in the compositions of the invention may be for example alkylene oxide polymers or copolymers, eg. poloxamers such as the Pluronics (eg. Pluronic F68 and 108 which are block copolymers of ethylene oxide and propylene oxide) or poloxamines such as the Tetronics (eg. Tetronic 908) and the Carbowaxes (which are polyethylene glycols (PEGs)), tyloxapol, polyvinylpyrrolidone, polyoxyethylene sorbitan fatty acid esters (Tweens), polysorbates (Spans), polyoxyl hydrogenated castor oil (Cremophore), polyoxyl stearates, alkylpolyoxyethylenes, PEG-modified phospholipids, and P-79. The preparation of P-79 is described in Example 2k of WO96/07437 which is herein incorporated by reference.

Preferably, the non-ionic surfactant emulsifier is P-79, especially preferably a poloxamer and most preferably a polyoxyethylene sorbitan fatty acid ester or polysorbate.

These will generally be used in relatively minor quantities, eg. 0.1 to 10% by weight relative to the weight of the aqueous phase of the composition, and are normally used at quantities sufficient to ensure that a stable dispersion can be formed, eg. 1 to 4% by weight.

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It will be realised that certain materials may function as both emulsifier and cloud point modifier, eg. PEGs. Accordingly it may be stated that the compositions according to the invention contain at least one non-ionic surfactant together with at least one different water-soluble non-ionic material in concentrations sufficient that a stable dispersion (one which does not settle out in less than 24 hours, preferably one which does not settle out in less than 6 months) of the flexible particles is formed in a dispersion medium having a cloud point above a steam sterilization temperature, eg. above 121°C, preferably in the range 90°C to 140°C, especially 121°C to 135°C. The total concentration of emulsifier and cloud point modifier will generally lie in the range 5 to 70% by weight, especially 8 to 30%, relative to the weight of the aqueous phase of the composition.

In the compositions of the invention, the dispersion medium is preferably substantially free from dissolved ionic species, eg. salts and other ionic excipients. This is important as the presence of such ionic species generally lowers the cloud point (the temperature at which phase separation of the non-ionic surfactant occurs) and may provoke aggregation of the suspended particles.

Desirably, the ionic strength of the dispersion medium is 0.5M or below, preferably 0.15M or below.

Since however parenteral administration of hypoosmotic fluids can provoke undesired effects, the medium will preferably be made substantially isotonic by the inclusion of physiologically tolerable non-ionic osmolality adjusting agents, eg. sugars and polyols such as sucrose, glucose and mannitol, or by the cloud point modifier itself.

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The particles in the compositions of the invention may be any flexible particles which have a desired diagnostic or therapeutic effect. Examples include droplets of insoluble iodinated liquids (eg. the X-ray contrast agents described in US-A-5260049), or fluorocarbons (eg. fluorocarbons such as are used in blood substitutes, for example perfluorodecalin), and vesicles containing or carrying a diagnostic or therapeutic agent (eg. the vesicles disclosed in PCT/GB96/01362, WO96/24381, US-A-5425366, WO96/25955, EP-A-458745, WO92/22298, US-A-5573751, WO95/26205, DE-A-4219723, PCT/GB95/02378 etc). Particularly preferably the particles are X-ray, MR, ultrasound or scintigraphic contrast agents, and especially preferably they are iodinated X-ray contrast agents.

The particles may be substantially neutrally charged (eg. to produce extended blood residence times) but may alternatively if desired carry a small net surface charge. In either event the cloud point modifier used according to the invention must be non-ionic and must be essentially free from ionic impurities (ie. no more than 1% wt, preferably no more than 0.5%, most preferably no more than 0.1% ionic impurity is generally permissible) in order to avoid modifying the surface charge of the particles.

The particles in the compositions of the invention may be of any size suitable for parenteral administration, eg. 5 to 8000 nm, but since the option for sterile filtration is not available for larger particles it is particularly preferred that the particles have a mean size of 100 to 8000 nm, especially 250 to 6000 nm. The particle concentration may be the conventional value for diagnostic or therapeutic efficacy for the particular particles chosen, eg. 0.05 to 50% by weight, preferably 0.5 to 20%, relative to the overall weight of the composition. Alternatively, the compositions may



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contain the particles at higher concentrations than are required on administration, and may be diluted, eg. with water for injections, saline, Ringer's solution, or a sugar solution, just before administration. For such dilution purposes, the diluent fluid need not be, but preferably is, non-ionic and/or isotonic.

However, as the dispersion medium used during the process of the invention it is preferred to use pyrogen-free water, eg. water for-injections.

Certain insoluble plant oils, eg. soya oil, do have cloud point modifying abilities. It is known that plant oils such as soya oil are contaminated with ionic phospholipids (such as lecithin), which are known to impart heat stability and charge to flexible particles (see US-A-5298262). However, as they represent mixtures of various different chemical species such plant oils are not desirable excipients for parenteral use.

Accordingly the compositions of the invention are preferably essentially free of such oils, eg. containing at maximum 0.5% by wt. plant oil.

Heat sterilization in the process of the invention may be carried out in a conventional fashion, eg. by autoclaving (steam or moist heat sterilization). Sterilization is preferably effected for at least 15 minutes, preferably 20 minutes or more, at a temperature of 121°C or slightly higher. In some cases, sterilization is performed at lower temperatures for longer times, eg. 110°C for 90 minutes. The cloud point modifiers of the invention are useful in such conditions.

The publications referred to herein are hereby incorporated by reference.

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The invention will now be described further by the following non-limiting Examples in which percentages and ratios are by weight unless otherwise stated.

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EXAMPLE 1NC 65373

NC 65373 is the sec-octyl ether of 2,4,6-triiodophenol. - It is prepared as described in Example 1 of US-A-5260049.

EXAMPLE 2

An emulsion of sesame oil was prepared by combining sesame oil, P-79, and water in a ratio of 10:2:88 (ie., 10% sesame oil, 2% P-79, and 88% water). (P-79, described in Example 2k of PCT/GB95/02109 is a PEG-double ester of molecular weight about 10 kD and formula  $\text{CH}_3(\text{CH}_2)_{14}\text{COO}(\text{CH}_2)_{15}\text{COO}((\text{CH}_2)_2\text{O})_n\text{CH}_3$ . The cloud point of P-79 is 104°C in the absence of modifiers). The resulting suspension was then passed through a Microfluidics M110S microfluidizer at 14,000 PSI at least 6 times. At the end of this process, the particle size of the emulsion was 196 nm. When this emulsion was autoclaved under standard conditions (ie. 121°C for 20 minutes), it took on the appearance of cottage cheese, being somewhat flocculated. Upon shaking, this appearance was broken and an emulsion of 229 nm was obtained (particle sizing by light scattering with a Horiba 901a particle sizer).

When the same process was repeated using 10% sesame oil, 2% P-79, 15% polyethylene glycol 1450, and 73% water, a droplet size of 139 nm was achieved after microfluidization. (15% polyethylene glycol 1450 is sufficient to raise the cloud point of P-79 to 128°C). After autoclaving at 121°C for 20 minutes, the emulsion emerged intact appearing fluid and in the same state as before heat sterilization. Particle size after autoclaving was 159 nm. Thus the addition of PEG 1450 at 15% removed the need for agitation after autoclaving to recover the emulsion state. This is a major process

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advantage in the preparation of such drug delivery vehicles.

For this Example, sesame oil was selected to produce a model emulsion system. For parenteral use, it would be replaced by a therapeutic or diagnostic agent oil or a combination of sesame oil and a therapeutic or diagnostic agent oil or other parenteral oils.

#### EXAMPLE 3

An emulsion was prepared as in Example 2 using 10% sesame oil, 15% NC 65373 (an iodinated contrast agent which is also an oil at room temperature), 2% P-79, and 15% PEG 1450 (58% water) with a droplet size of 196 nm. Upon autoclaving, the emulsion retained its appearance with a particle size of 216 nm without agitation of the sample. Thus, even with a total of 25% oil, the addition of the non-ionic cloud point modifier, PEG 1450, afforded an autoclavable emulsion.

#### EXAMPLE 4

The cloud point of solutions of 2% P-79 and 3% tyloxapol with added non-ionic cloud point boosters propylene glycol and PEG 1450 were determined and the results are set out graphically in Figures 1 and 2 of the accompanying drawings.

#### EXAMPLE 5

##### Micelles and Nonionic Cloud Point Modifiers: elevation of the Cloud Point

Micelles are defined as thermodynamically stable aggregates of amphiphilic molecules in solution. The amphiphilic molecules may be ionic (ie. cationic, anionic, or zwitterionic) depending on the charge

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associated with the hydrophilic moiety of the molecule or the "head group". Another large class of amphiphilic molecules is nonionic in character having either polyhydroxy or polyoxyethylene oxide polar moieties. These molecules aggregate into micelles and can solubilize otherwise water insoluble molecules such as therapeutic and diagnostic agents. Unlike the ionic micelles, these aggregates undergo a distinct phase separation at elevated temperatures known as the cloud point. Inasmuch as any water insoluble molecules solubilized within the micellar phase of the solution will also separate into the surfactant phase above the cloud point, it is not clear whether this physical phenomenon is detrimental to the use of nonionic micelles for drug solubilization. However, the "resolubilization" of surfactant as the temperature is lowered below the cloud point and the distribution of the solubilized drug within the micelle phase is uncontrolled and may afford precipitated drug/agent or liquid crystalline preparations rather than micelles as desired. Thus, being able to avoid phase separation during heat sterilization of parenteral micelle preparations is viewed as an advantage. In addition, the use of molecules envisaged in this invention will provide more nearly iso-osmotic and isotonic preparations with the plasma of the body.

Table 1 illustrates the impact of nonionic cloud point modifiers (i.e. PEG 1450, and propylene glycol) on a 3% (wt/vol%) solution of nonionic surfactant, Tyloxapol, which is above the critical micelle concentration (cmc). It is apparent from the data that the addition of nonionic cloud point modifiers avoids phase separation during heat sterilization and maintains the micelles in their conventional form.

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**Table 1.**  
**Impact of Propylene Glycol and PEG 1450 on the Cloud**  
**Point of a 3% Solution of Tyloxapol.**

Cloud Point Modifier Concentration (%)	Propylene Glycol (Cloud Point °C)	PEG 1450
1.0	100	
2.5	104	
5.0	109	103
7.5	115	108
10.0	125	112
15.0		123

Table 2 below illustrates the effect of the addition of nonionic cloud point modifiers upon the cloud point of a 2% (wt/vol%) solution of the nonionic, polymeric surfactant P-79. Both nonionic cloud point modifiers are able to elevate the cloud point of a 2% solution of P-79 above that require for steam sterilization (e.g. 121°C). Also, this level of P-79 is above the cmc and thus micelles are present in the solution.

**Table 2**  
**Impact of Propylene Glycol and PEG 1450 on the Cloud**  
**Point of a 2% Solution of P-79**

Cloud Point Modifier Concentration (%)	Propylene Glycol (Cloud Point °C)	PEG 1450
2.0	110	
5.0	115	110
7.5	122	
10.0	124	118
15.0		128

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Further, some contrast agents and some therapeutic drugs are in themselves nonionic amphiphilic molecules such that they will aggregate into micelles in aqueous solution and will exhibit the same cloud point behavior as more conventional nonionic surfactants. These types of nonionic micelles will also benefit from the addition of nonionic cloud point modifiers and accompanying heat sterilization.

#### EXAMPLE 6

##### The Use of Nonionic Cloud Point Modifiers to Aid in the Steam Sterilization of Nonionic Liposomes

Liposomes are hollow spheres of phospholipids arranged in a bilayer such that there are aqueous media both inside and outside the membrane/liposome. While several phospholipids are neutral inasmuch as they exhibit a net charge of zero, they are still zwitterionic molecules (eg. lecithin). Thus, in general, liposomes are charged particles. However, the process of making these particles "invisible" to the defense systems of the body requires the use of polyethylene oxide (PEG) modified phospholipids to effectively mask the charge of the liposome and make them act like nonionic particles. Thus the use of nonionic cloud point modifiers may further benefit these "stealth" liposomes with respect to steam sterilization.

For example, liposomes can be prepared at a concentration of 1.2% lecithin, 0.8% dimyristylphosphatidyl glycerol (DMPG) and 0.5% dipalmitoylphosphatidyl ethanolamine conjugated to PEG or methoxy PEG 5000 (molecular weight). In the absence of a nonionic cloud point modifier, heat sterilization of these particles would not be expected to be successful due to unacceptable particle size growth and aggregation. However, with preparation of these same

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liposomes in the presence of enough nonionic cloud point modifier to elevate the cloud point of the nonionic phospholipid (ie. the PEGylated phospholipid), the liposomes should survive steam sterilization. It is important to point out that inasmuch as these particles are "hollow", the nonionic cloud point modifier should be both inside and outside the phospholipid membrane. This is to maintain an equiosmolar concentration across the membrane. Without this, the osmotic pressure may be enough to cause the liposomes to shrink due to water transport to the outside of the membrane where the concentration of nonionic cloud point modifier is higher.

It may be noted that P-79 can be used to "stealth" these types of liposomes and that the cloud point of this nonionic surfactant can be elevated above the temperature required for steam sterilization.

#### EXAMPLE 7

##### Echogenic Contrast Agent

Polymer microbubbles are prepared by generating an emulsion using 5 mL of 5% P-73 (a membrane forming polymer having the repeat unit  $-O(CH_2)_{15}COOCH(CH_3)O.CO.(CH_2)_{15}O.CO.(CH_2)_4CO-$  prepared as described in Example 2a of WO96/07434) in camphene and 15 mL of a solution in water of 1% P-79 and 15% PEG 1450. Emulsification is carried out at 50-60°C with an Omni-Mixer homogenizer equipped with a 20 mm OD generator at 5000 rpm for 4 minutes. The emulsion is decanted into 10 mL Wheaton Type I tubing vials filling to about 4 mL. The vials are placed in a FTS DuraStop MP lyophilizer where the shelf temperature is pre-cooled to -50°C. After two hours freezing time, shelf temperature is raised to -20°C for primary drying under



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300 m torr for 36 to 48 hours. Shelf temperature is then raised to -5°C for secondary drying for about 4 hours. The lyophilised product is reconstituted by adding glucose solution to give a total concentration of 10 mg/mL (or 1%) for P-73 and P-79 combined and an isotonic aqueous phase. The product is then steam sterilized at 121°C for 20 minutes.

Claims

1. A diagnostic or therapeutic composition comprising physiologically tolerable, diagnostically or therapeutically effective flexible particles and a physiologically tolerable non-ionic surfactant emulsifier in an aqueous dispersion medium, characterised in that said aqueous dispersion medium further contains a physiologically tolerable, non-ionic, water-soluble cloud point modifier at a concentration such that the cloud point of said medium is above a temperature usable for steam sterilization.
2. A composition as claimed in claim 1 wherein the cloud point of the medium is above 90°C.
3. A composition as claimed in claim 2 wherein the cloud point of the medium is above 121°C.
4. A composition as claimed in any one of claims 1 to 3 wherein said cloud point modifier is a polyethylene glycol, propylene glycol, monoalcohol, polyol or cyclodextrin.
5. A composition as claimed in claim 4 wherein said cloud point modifier is PEG 1450 or propylene glycol.
6. A composition as claimed in any one of claims 1 to 5 wherein said cloud point modifier is present in an amount of 1 to 30% by weight, relative to the weight of the aqueous phase.
7. A composition as claimed in claim 6 wherein said cloud point modifier is present in an amount of 5 to 20% by weight, relative to the weight of the aqueous phase.
8. A composition as claimed in any one of claims 1 to 7 wherein said surfactant emulsifier is a poloxamer,

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poloxamine, tyloxapol, polyvinylpyrrolidone, polyoxyethylene sorbitan fatty acid ester, polysorbate, polyoxyl hydrogenated castor oil, polyoxyl stearate, alkylpolyoxyethylene, PEG-modified phospholipid or P-79.

9. A composition as claimed in claim 8 wherein said surfactant emulsifier is P-79, a poloxamer, a polyoxyethylene sorbitan fatty acid ester or a polysorbate.

10. A composition as claimed in claim 9 wherein said surfactant emulsifier is a polyoxyethylene sorbitan fatty acid ester or a polysorbate.

11. A composition as claimed in any one of claims 1 to 10 wherein said surfactant emulsifier is present in an amount of 0.1 to 10% by weight, relative to the weight of the aqueous phase.

12. A composition as claimed in claim 11 wherein said surfactant emulsifier is present in an amount of 1 to 4% by weight, relative to the weight of the aqueous phase.

13. A composition as claimed in any one of claims 1 to 12 wherein the dispersion medium is substantially free from dissolved ionic species.

14. A composition as claimed in any one of claims 1 to 13 wherein the dispersion medium is isotonic.

15. A composition as claimed in any one of claims 1 to 14 wherein said flexible particles comprise X-ray, MR, ultrasound or scintigraphic contrast agents.

16. A composition as claimed in claim 15 wherein said flexible particles comprise iodinated X-ray contrast agents.

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17. A composition as claimed in any one of claims 1 to 16 wherein said flexible particles have a mean size of 100 to 8000 nm.

18. A composition as claimed in claim 17 wherein said flexible particles have a mean size of 250 to 6000 nm.

19. A composition as claimed in any one of claims 1 to 18 wherein said flexible particles are present in an amount of 0.05 to 50% by weight, relative to the weight of the composition.

20. A composition as claimed in claim 19 wherein said flexible particles are present in an amount of 0.5 to 20% by weight, relative to the weight of the composition.

21. A process for the preparation of a sterile aqueous dispersion as claimed in any one of claims 1 to 20, said process comprising heat sterilizing a composition comprising physiologically tolerable, diagnostically or therapeutically effective flexible particles and a physiologically tolerable non-ionic surfactant emulsifier in an aqueous dispersion medium, characterised in that said aqueous dispersion medium further contains a physiologically tolerable, non-ionic, water-soluble cloud point modifier at a concentration such that the cloud point of said medium is above the steam sterilization temperature.

22. A process as claimed in claim 21 wherein the heat sterilisation is conducted at 121°C or higher.

23. The use of heat sterilized compositions according to any one of claims 1 to 20 in therapy or diagnosis.

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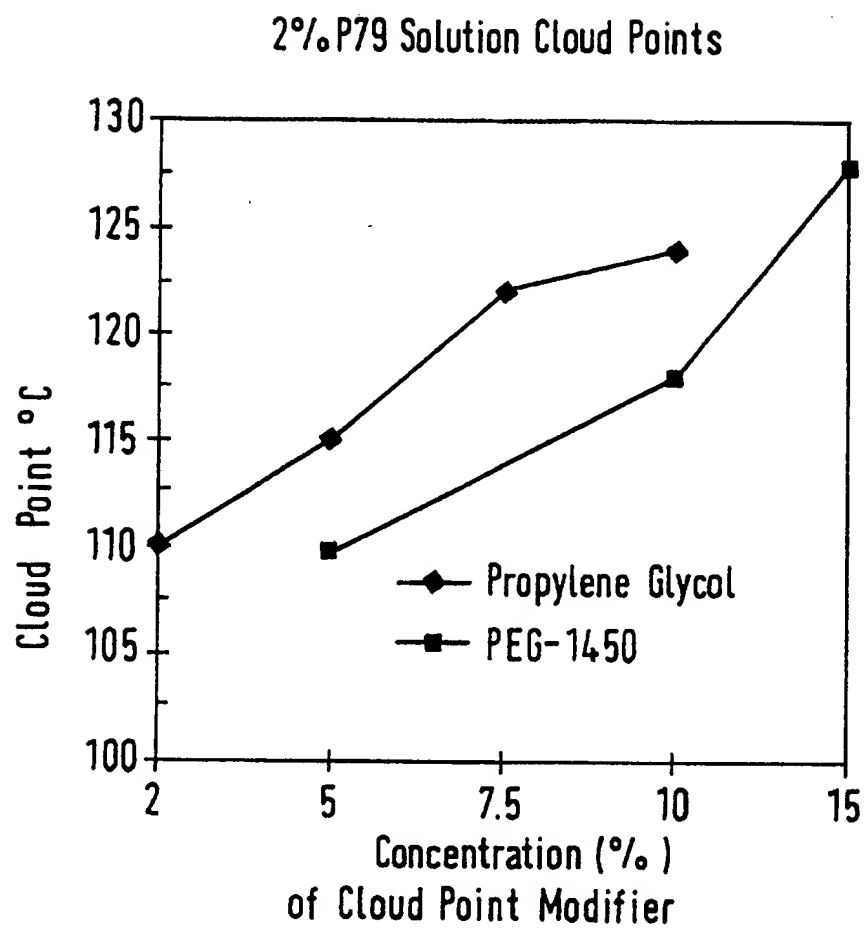


FIG. 1.

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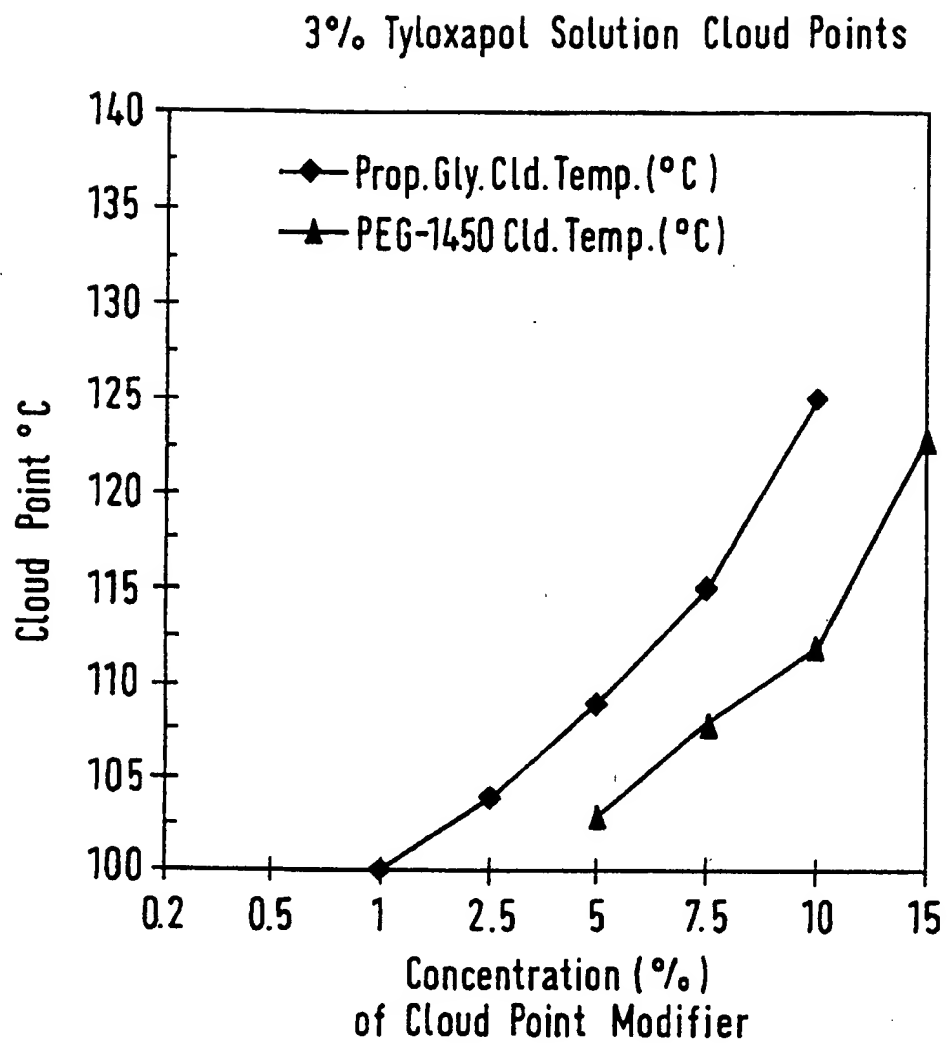


FIG. 2.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB 98/00778

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 A61K47/10 A61K47/26 A61K47/34

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 601 619 A (STERLING WINTHROP INC) 15 June 1994 see page 5, line 26 - line 27 see claims 1-11 ----	1-23
X	EP 0 602 700 A (STERLING WINTHROP INC) 22 June 1994 see page 5, line 44 - line 56 see claims 1-20 ----	1-23
X	EP 0 605 024 A (STERLING WINTHROP INC) 6 July 1994 see page 5, line 38 - line 55 see page 1-9 ---- -/-	1-23

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3018

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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB 98/00778

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
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